Clot-Inducing Minerals Versus Plasma Protein Dressing for Topical Treatment of External Bleeding in the Presence of Coagulopathy

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Background: Previous studies identified WoundStat (WS, smectite) and Combat Gauze (CG, kaolin-coated gauze) as the most effective available agents for controlling arterial bleeding with potential utility in casualty care. Tissue sealant properties of WS suggested its potential advantage over clot-promoting CG for treating coagulopathic bleeding. This study compared the efficacy of CG and WS with a fibrinogen-based (FAST) dressing to control bleeding in coagulopathic animals.

Methods: Coagulopathy was induced in pigs (n = 55, 35 kg) by ∼50% isovolemic hemodilution and hypothermia (core temperature, 33°C ± 0.5°C). A 6-mm arteriotomy was made in the femoral artery and free bleeding allowed for 30 seconds. A test agent (n = 13–15 per group) or control product (gauze, GZ, n = 12) was applied to the wounds and compressed with a Kerlix gauze for 2 minutes. Fluid resuscitation was given, titrated to a mean arterial pressure of 65 mm Hg. Animals were observed for 180 minutes or until death. Angiography using the computed tomography method was performed on survivors, and local tissues were collected for histology.

Results: No differences were seen in baseline measures. Coagulopathy, confirmed by a 31% increase in prothrombin time and a 28% reduction in clotting strength (maximum amplitude, thrombelastography assay), was similar in all groups before injury. The average pretreatment blood loss was 11.9 mL/kg ± 0.4 mL/kg with no difference among groups. Posttreatment blood loss, however, was significantly different (p = 0.015) ranging from 18.2 mL/kg ± 8.8 mL/kg (FAST) to 63.3 mL/kg ± 10.2 mL/kg (GZ controls). Stable hemostasis was achieved in 10 of 13 (FAST), 5 of 15 (CG), 2 of 15 (WS), and 1 of 12 (GZ) animals in each group, resulting in significantly different survival rates (8–77%; p = 0.001). The average survival times were 145 (FAST), 119 (CG), 75 (WS), and 74 (GZ) minutes for different groups (p < 0.002). The outcomes with the FAST dressing were significantly better than with WS or GZ in this coagulopathic bleeding model. Essentially, no difference was found between WS and GZ control. Computed tomography images showed limited blood flow only through the vessels treated with FAST dressings. Histologic observations of the vessels indicated minimal damage with FAST and CG and greater injury with WS with some residues present on the tissues.

Conclusion: The tissue sealant property of WS is apparently mediated by clot formation in the wound; therefore, it was ineffective under coagulopathic conditions. CG was partially effective in maintaining blood pressure up to 1 hour after application. FAST dressing showed the highest efficacy because of the exogenous delivery of concentrated fibrinogen and thrombin to the wound, which bypasses coagulopathy and secures hemostasis.

Key Words: Combat Gauze, WoundStat, Fibrinogen/fibrin dressing, Coagulopathy, Swine, FAST dressing.

Uncontrolled hemorrhage remains the leading cause of potentially preventable death in combat casualties.[1,2] In the current conflict, nearly two-thirds of these deaths occurred as a result of torso injuries with noncompressible hemorrhage and one-third from extremity injuries with compressible hemorrhage.[3] These statistics once again emphasize the urgent need for developing better methods to control hemorrhage in the field and in the operating rooms to potentially reduce war mortality. Massive trauma and hemorrhage, if it is not treated promptly, can also lead to the lethal triad of life-threatening coagulopathy: hypothermia, metabolic acidosis, and inability to form hemostatic clots.[4,5] Even when eventually controlled, significant blood loss leaves the victims vulnerable to shock, sepsis, and multiple organ failure.[6,7]

In the military arena, trauma and hemorrhage from massive tissue injuries caused by explosion, resuscitation with hydroxyl ethyl starch (HES) containing colloids or large volume of crystalloids (hemodilution), delayed evacuation and transport in helicopters (hypothermia), and hypoperfusion/shock (metabolic acidosis) have collectively created conditions that can induce early coagulopathy in some casualties. Among the combat casualties who required blood transfusion, one-third (38%) were diagnosed with acute traumatic coagulopathy at an international normalized ratio ≥1.5 on arrival to a combat support hospital. High mortality (24%) was associated with early coagulopathy and acidosis in these patients.[8] A diffuse large area of bleeding associated with some vascular injuries in coagulopathic patients is much harder to treat with ordinary hemostatic agents than defined

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bleeding in noncoagulopathic patients, mainly because most hemostatic agents stimulate the clotting function of the patients' own blood.[9]

Previous experimental studies identified two new hemostatic agents, WoundStat (WS) and Combat Gauze (CG), among a number of novel products as the most powerful agents currently available for controlling external hemorrhage with potential use in combat and civilian trauma.[10–13] The two agents, one in granular form (WS) and the other one in gauze (CG), were equally effective in stopping hemorrhage and preventing exsanguination of swine subjected to lethal arterial injuries with 100% and 80% survival rates, respectively. In vitro experiments also confirmed the high in vivo efficacy of these agents. The mineral components of these agents (smectite and kaolin, respectively) were found to be potent clot-inducing chemicals when added to the blood.[10,11] The known sealant properties of smectite clay that form when the dry minerals are mixed with water or blood suggested a possible hemostatic advantage of WS for treatment of coagulopathic bleeding that may not be possible with other hemostatic agents. This hypothesis was supported by some in vitro results using human blood samples.[14–16]

Therefore, this study was performed to analyze the hemostatic efficacy of WS in coagulopathic subjects and to assess the risk/benefit of using this material to control hemorrhage in trauma patients with acquired coagulopathy. The effect of WS was compared with CG, a clot-inducing agent only, and a biological dressing (FAST, prototype) that contains precursors of hemostatic clots (thrombin, fibrinogen, and factor XIII). The fibrin formation, and thereby the hemostatic activity of FAST dressing, is mostly independent of blood in the wound; therefore, it is expected to function even under coagulopathic conditions (positive control). Regular gauze was also included for comparison purposes as a negative control agent.

MATERIALS AND METHODS

This study was approved by the Animal Care and Use Committee of the US Army Institute of Surgical Research. All animals received care and were used in strict compliance with The Guide for the Care and Use of Laboratory Animals.[17]

WS and CG were purchased from commercial sources (without the need for prescription). Both products have been cleared for marketing by the US Food and Drug Administration (FDA) and indicated for temporary treatment of external wounds to control moderate to severe bleeding. WS and CG are supplied in sterile packages in the amounts sufficient to treat an average-sized wound. Because these products are not biodegradable, they must be removed from the wound entirely before surgical repair and closure of skin. The FAST dressing was donated by the manufacturing company (STB Lifesaving Technologies) through a material transfer agreement between the US Army Institute of Surgical Research and STB. These prototype dressings (10 cm × 10 cm) were made primarily of a mixture of plasma-derived human fibrinogen and thrombin proteins that were freeze-dried as a single layer on an absorbable backing material. Other clotting and stabilizing components such as factor XIII and albumin were

also present in the dressings. The control agent used in the study was 4 in × 4 in sterile gauze pad that had a similar composition as the raw material for CG (50% rayon + 50% polyester). Several of these gauzes (n = 10), weighing equal to one CG (~18 g), were used for each control treatment.

In Vivo Methods

Yorkshire cross-bred pigs (castrated males only) weighing 32 kg to 40 kg were purchased from Midwest Research Swine and used in this study. On arrival, the animals were housed and observed for 5 days to be acclimated and exclude the possibility of preexisting disease. Before the surgery date, venous blood samples were collected from pigs (percutaneously); complete blood counts (CBC), standard coagulation tests (prothrombin time [PT], activated partial thromboplastin time [aPTT], and fibrinogen), and serum chemistry profile were measured to ensure the health and normal values of the animals. Pigs were fasted for 12 hours to 18 hours before the surgery with free access to water. On the day of surgery, pigs were induced, intubated, and anesthetized by inhalation anesthesia (isoflurane) and mechanical ventilation as described before.[10] During instrumentation and laparotomy procedures, maintenance fluid (lactated Ringer's, LR), was administered to the pigs at 5 mL/kg/hr through a venous line placed in an ear vein. The pig's body temperature was monitored by placing a probe in the rectum and maintained between 37°C and 39°C, with the use of a water-filled warming blanket until hemodilution was started.

Surgical Procedures

The right carotid artery and the jugular vein were cannulated (via a cut down) to monitor and record various vital signs (systolic, diastolic, mean arterial pressure [MAP], and heart rate), draw blood samples (arterial), and infuse resuscitation fluid. Next, a midline laparotomy was performed, followed by a splenectomy to eliminate the possibility of auto transfusion of red cells by the pig's contractile spleen during bleeding. The blood loss volume from the splenectomy was replaced by infusing LR at three times the weight of the spleen. A cystostomy was also performed to aid in the drainage of urine. The abdomen was then closed with sutures, and the skin was stapled.

Next, the right femoral artery was cannulated for blood-fluid exchange and induction of dilutional coagulopathy. To create injury and bleeding, we isolated a segment of the contralateral (left) femoral artery (~5 cm) in the groin area and removed the overlying abductor muscle. The vessel was then covered with a small piece of gauze saturated with 2% lidocaine to relax vasospasm and prevent tissue drying during subsequent procedures. Baseline blood samples were next collected from the carotid arterial line for CBC, coagulation, and arterial blood gas (ABG) analysis.

Coagulopathy Induction

Hypothermia and dilutional coagulopathy were induced as previously described.[18] Briefly, 60% of the circulating blood volume in each pig was estimated based on the body weight (total blood volume = 7% body weight) and was withdrawn from the femoral artery catheter at the rate of 50

mL/min using a peristaltic pump. The blood removed was simultaneously replaced with an equal volume of room temperature Hextend solution, which was infused into the pig's jugular vein at the same rate. This blood-fluid exchange had minimal effects on the heart rate and blood pressure of the animals. As blood draw and fluid infusion were done simultaneously, the final hemodilution levels in animals were close to 50%. The pig's body temperature was allowed to drop gradually during the hemodilution, and the blanket underneath was also cooled to achieve hypothermia at a target temperature of 33°C ± 0.5°C. After 10-minute stabilization at hypothermic temperature, animals' hemodynamic values were recorded; blood samples were collected to measure CBC, ABG, and coagulation parameters. A stable MAP of 60 mm Hg or higher was required before the rest of the experiment could proceed. An additional citrated blood sample was also collected for the thrombelastography (TEG) measurements, as described below. The maintenance fluid was discontinued at this point.

Vascular Injury and Treatment

To create hemorrhage, a 6-mm diameter arteriotomy was produced on the exposed surface of the vessel as described before,[10] and unrestricted bleeding was allowed for 30 seconds. The blood shed during this period was collected by suction, weighed, and recorded as pretreatment blood loss. After this initial hemorrhage, wounds were treated with one package of each test agent (randomly selected) to control the bleeding. A 3-minute total treatment time was set for all the agents. The packing of wounds with CG, WS, and regular gauze took ~1 minute to complete but application of FAST dressing to the wound was immediate. All the materials except the FAST dressing were covered with a roll of gauze (Kerlix) and pressed against the wound for 2 minutes to establish hemostasis. Compression time for the FAST dressing was extended to 3 minutes to equalize the total treatment time for all the agents. The FAST dressings were pressed with the hand without using Kerlix because this method produced better conformity and attachment of the thin dressing to the tissues. In addition, placing the gauze required momentary release of the dressing, which could have irreversibly disrupted the weak bonding of the fibrin layer with the injured tissues. To minimize variability, the vascular injury, dressing application, and compression procedures for all the experiments were done by the same investigator (BK). The identity of the test material for each experiment was also hidden from the surgeons until the time of application.

After 30 seconds of compression, fluid resuscitation was started by infusing 500 mL of Hextend to replace the initial pretreatment blood loss. The colloid fluid was administered intravenously at 100 mL/min and targeted to raise the MAP to 65 mm Hg, the average baseline blood pressure of anesthetized pigs. Compression was stopped after 2 minutes and hemostasis observed for 3 minutes without removing the gauze. If rebleeding occurred during this period, the gauze was removed and another package of the test agent was applied to the wound. The 2-minute compression was then repeated with new Kerlix gauze. FAST dressing compression was performed without the use of gauze; however, during the

observation period, these dressings were also covered with gauze to produce a similar condition. Wounds were treated twice at most (if needed) with each product regardless of hemostatic outcome. After treatment, hemostasis was observed for the next 3 hours with the Kerlix gauze left in place. Fluid administration was continued with LR (100 mL/min, maximum of 10 L) as needed to raise and maintain the MAP between 60 mm Hg and 65 mm Hg throughout the experiment. Any shed blood during this period was collected and measured as posttreatment blood loss. Animals were monitored up to 3 hours or until death as determined by end-tidal pCO_2 <15 mm Hg and MAP <20 mm Hg. Final blood samples (arterial) were collected for hematological measurements before killing the animals.

The inclusion criteria for selection of pigs included normal (1) hematocrit (30–40%), (2) platelet count (≥200 K/mm^3), and (3) coagulation values (PT, ≤12 seconds; PTT, ≤24 seconds; and fibrinogen, ≥100 mg/dL). The exclusion criteria included (1) persistent hypotension (MAP <60 mm Hg) before or after hemodilution and hypothermia, (2) misapplication of an agent including failure to control bleeding during the compression phase to allow hemostatic reactions to occur, and (3) persistent hypotension after successful hemostatic treatment (unresponsiveness of MAP to fluid administration because of increased vascular permeability).

Surviving animals, which remained anesthetized, were scanned by the computed tomography method, and images of arterial blood flow in both legs (treated and untreated) were obtained. Next, the treated legs of the surviving pigs were flexed and stretched five times, mimicking walking to test the stability of the hemostasis. At the conclusion of experiments, the product was removed from the wound, and the status of injury and patency of the vessel was examined. Animals were then killed; local vascular, muscle, and nerve tissues were collected and examined histologically as described before.[10] Briefly, histologic slides were prepared from recovered tissues according to standard procedure and stained with hematoxylin and eosin by the technicians. The slides were coded and delivered to a board certified veterinarian pathologist (J.S.E) who was blinded to the treatment group for histologic observation and evaluation. Once the examination of individual slides was completed, the codes were broken and the results were categorized under each specific hemostatic product and reported.

In Vitro Methods

TEG analysis was used to determine the effect of each clot-inducing agent on the in vitro coagulation of hemodiluted samples. The FAST dressing was not tested because of a technical problem. When blood is mixed with FAST dressing, protein components of FAST dressing (fibrinogen and thrombin) are dissolved in the blood, giving an unfair advantage to this product when this blood is tested. The clot-inducing agents, however, are removed from the blood sample before TEG analysis. To prepare the test materials, we cut out 2-mm diameter circular pieces from the dressing (CG and regular gauze) with a punch biopsy instrument. Blood samples were collected from each pig at the baseline and after hemodilution in citrate anticoagulant. The hemodiluted samples were divided into four aliquots from which three were

treated with different hemostatic agents. Ten milligrams of each dressing pieces or WS granules were added to blood aliquots and gently inverted eight times. Three hundred forty microliters of these treated blood samples plus aliquots of an untreated diluted and normal (baseline) blood samples were placed in TEG cups and allowed to clot spontaneously (contact activation). To initiate coagulation, 20 μL of calcium chloride (0.2 mol/L) was added to the samples to overcome the anticoagulant effect. TEG analysis was performed at 37°C. Each sample was tested in triplicate, and the coagulation tracing continued for at least 30 minutes after the clot reached maximum strength. The regular TEG parameters, including reaction time (min), clotting time (min), angle (α, degree), and maximum amplitude (mm) as well as percentage of fibrinolysis at 30 minutes postclot maturation (LY30) were determined in each sample as described before.

Data Analysis

Data are expressed as a mean ± SEM and analyzed by one-way analysis of variance, Fisher's exact test, and the log rank for statistical comparisons. The *p* values were adjusted according to the false discovery rate method for bigroup comparison by using the Tukey test.[19] The data with high variance were log-transformed for analysis of variance analysis. The nonparametric data were analyzed by using the Newman-Keuls multiple comparison test, and the bigroup comparison was done by using Dunnett's test. A *p* < 0.05 was considered statistically significant.

RESULTS

In Vivo

No difference was found in baseline physiologic and hematological measurements among treatment groups. The averages of these measures for all the animals are shown in Table 1 (baseline column). Each new agent was tested in 15 pigs, but the data from two animals in the FAST dressing group were excluded because of an application error in one case (bleeding could not be stopped during compressions) and persistent hypotension (unresponsive to fluid resuscitation) in another animal with successful dressing treatment. These conditions were part of predefined exclusion criteria in the study.

Coagulopathy Induction

Approximately 50% hemodilution with Hextend had no significant effect on acid-base balance in the blood of all the pigs (Table 1). The lactate level in FAST group was 25% higher than the other groups but it was within normal range for pigs. The hemodilution, however, reduced RBC (50%), hemoglobin (51%), and plasma fibrinogen concentration (52%) almost equally in all groups as expected (Table 1). Changes in these parameters corresponded to the degree of hemodilution; however, in the case of platelets, it resulted in ~72% decrease in the counts of all groups. This decrease is perhaps due to a side effect of HES in Hextend. A larger reduction of platelet counts was also seen in rabbits that were hemodiluted with Hextend but not with 5% albumin solution.[20] PT and aPTT were measured in whole blood at 37°C. The hemodilution prolonged the PT by 31% but had no effect on aPTT. The ratio of PT after hemodilution over baseline (equivalent to international normalized ratio in clinical samples) was 1.3. There were no differences in coagulation measurements, cell counts, or hypothermic temperatures among the groups after hemodilution and hypothermia induction.

Clotting profiles (TEG tracings) of normal blood (collected at baseline), diluted blood samples (collected after hemodilution), and diluted blood treated with different hemostatic agents in vitro are shown in Figure 1. The traces

TABLE 1. Physiological and Hematological Measures in Pigs at Baseline and at Preinjury (Post Hemodilution and Hypothermia) Time Point

Measure	Baseline Combined Groups (n = 55)	Preinjury				Overall *p* Value
		Gauze (GZ; n = 12)	WoundStat (WS; n = 15)	Combat Gauze (CG; n = 15)	Fibrin Sealant (FAST; n = 13)	
Body weight (kg)	35.3 ± 0.3	—	—	—	—	—
Temperature (°C)	37.7 ± 0.1	32.7 ± 0.1	32.7 ± 0.0	32.6 ± 0.0	32.9 ± 0.1	0.2
MAP (mm Hg)	70.3 ± 1.5	64.2 ± 1.4	66.4 ± 1.3	65.8 ± 1.5	61.8 ± 0.6	0.06
RBC ($10^6/\mu$L)	5.5 ± 0.1	2.8 ± 0.1	2.7 ± 0.1	2.8 ± 0.0	2.7 ± 0.0	0.7
Hemoglobin (g/dL)	9.5 ± 0.1	4.7 ± 0.2	4.6 ± 0.1	4.9 ± 0.1	4.6 ± 0.1	0.2
Platelet (1,000/μL)	385 ± 12	107 ± 9	102 ± 5	107 ± 8	118 ± 9	0.5
PT (sec)	13.1 ± 0.1	16.8 ± 0.3	17.5 ± 0.5	17.5 ± 0.4	16.9 ± 0.2	0.4
aPTT (sec)	22.4 ± 0.3	21.0 ± 0.7	22.9 ± 0.6	20.8 ± 0.4	22.3 ± 0.7	0.04
Fibrinogen (mg/dL)	268 ± 7	129 ± 7	125 ± 9	133 ± 7	129 ± 7	0.9
pH	7.42 ± 0.01	7.47 ± 0.01	7.45 ± 0.01	7.44 ± 0.01	7.43 ± 0.01	0.02
Lactate (mM)	2.4 ± 0.1	2.8 ± 0.2	2.8 ± 0.1	2.6 ± 0.1	3.5 ± 0.2*	<0.01
Base excess (mM)	5 ± 0.3	6.6 ± 0.5	5.7 ± 0.5	5.9 ± 0.4	5.1 ± 0.5	0.3

Data are expressed as mean ± SEM and analyzed by one-way analysis of variance test. No significant difference was found in the baseline measurements among groups; therefore, the averages for all animals are listed in the table. The *p* values in the table represent comparisons of measurements after hemodilution and hypothermia among groups. PT and aPTT were determined in whole blood, but fibrinogen concentration was measured in plasma sample.

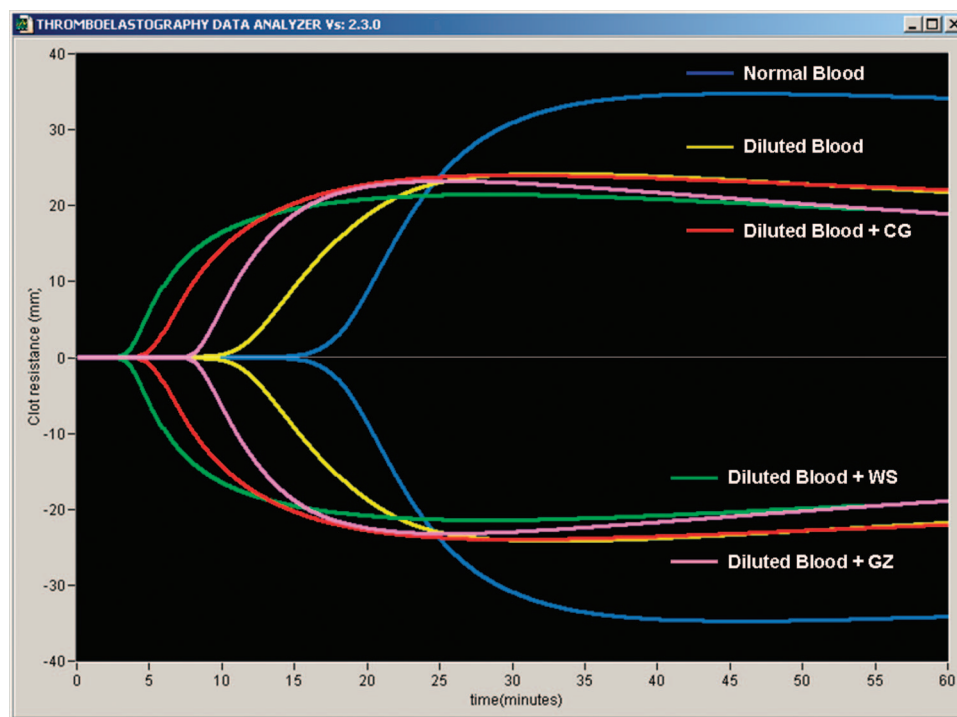* *p* < 0.05 vs. other treated group.

Figure 1. The average thrombograms of pig blood at baseline (normal blood), after hemodilution, and after in vitro treatment with different hemostatic agents. Two milliliters of citrated blood samples were mixed with 10 mg of each agent, and intrinsic coagulation was initiated by addition of calcium chloride.

TABLE 2. TEG Analysis of Normal and In Vivo Diluted Blood Samples Before (Untreated) and After Exposure to Hemostatic Agents

TEG Parameter	Normal Blood	Diluted Blood (Untreated)	Diluted Blood + WS	Diluted Blood + CG	Diluted Blood + GZ
Reaction time (min)	14.8 ± 0.5	9.5 ± 0.4*	$3.0 \pm 0.1^{\dagger\ddagger}$	$4.3 \pm 0.2^{\dagger\ddagger}$	$7.3 \pm 0.5^{\dagger\S}$
Clotting time (min)	3.7 ± 0.2	4.1 ± 0.3*	$2.9 \pm 0.3^{\dagger}$	$2.6 \pm 0.2^{\dagger}$	$2.8 \pm 0.3^{\dagger}$
Angle (°)	50.2 ± 1.3	44.3 ± 1.7*	$55.6 \pm 2.4^{\dagger}$	$55.4 \pm 2.0^{\dagger}$	$53.8 \pm 2.0^{\dagger}$
Maximum amplitude (mm)	68.1 ± 0.7	48.8 ± 1.3*	$39.4 \pm 1.3^{\dagger\ddagger}$	$46.0 \pm 1.4^{\ddagger\S}$	$47.8 \pm 1.8^{\ddagger\S}$
LY 30 (%)	0.9 ± 0.2	2.1 ± 0.5*	$3.1 \pm 0.5^{\ddagger}$	$2.4 \pm 0.4^{\ddagger}$	$3.7 \pm 0.4^{\ddagger}$

Data expressed as mean ± SEM. The TEG values of normal blood (drawn at baseline) were compared with those of untreated diluted blood (drawn after hemodilution) using two-tailed unpaired t-tests. The TEG values of treated hemodiluted samples were compared with those of the untreated hemodiluted or normal blood samples using a one-way ANOVA test and followed by a Tukey test for pair group comparison.

* Values were significantly different ($p < 0.01$) from normal blood (*t* test).
† Values were significantly different ($p < 0.05$) from untreated diluted blood.
‡ Values were significantly different ($p < 0.01$) from normal blood.
§ Values were significantly different ($p < 0.05$) from WS-treated sample.

represent the average measurements of arterial blood samples collected from six pigs from different groups.

As expected, significant hemodilution (50%) slowed the kinetics of clot formation (smaller angle and longer clotting time) and decreased the strength of the clot (maximum amplitude), both indicating the reduced clotting capacity of the samples (Table 2). The percentage of fibrinolysis (LY30) of these less dense blood clots was also higher than normal clots in undiluted blood. The initial reaction, however, was faster (shorter reaction time) in the hemodiluted than in the normal samples. In vitro treatment of diluted blood samples with different hemostatic agents, including

gauze, further decreased the reaction time and accelerated the kinetics of clot formation but did not improve the diminished clot strength. In the case of WS, the clot strength was further decreased after the in vitro treatment (Table 2).

Hemostasis Achievement

The incidence of immediate hemostasis achievement (bleeding ceased with the first treatment) ranged from 8% (gauze) to 33% (CG). These initial hemostasis were not always stable during the experiment; for example, slow rebleeding occurred in two CG-treated pigs after initial hemostasis, but it eventually stopped thereby allowing the

TABLE 3.   Outcomes of Treating a Groin Arterial Hemorrhage With Different Hemostatic Dressings in Coagulopathic Swine

Outcome	Regular Gauze (GZ; n = 12)	WoundStat (WS; n = 15)	Combat Gauze (CG; n = 15)	Fibrin Sealant (FAST; n = 13)	Overall *p* Value
Stable hemostasis achieved	1/12	2/15	5/15	10/13*	<0.001 (χ^2)
Total time bleeding stopped (min)	13.7 ± 8.9	28.2 ± 16.2	75.8 ± 21.6	113.3 ± 25*	0.02 (Kruskal-Wallis)
Pretreatment blood loss (mL/kg)	13.5 ± 0.8	11.5 ± 0.8	11.5 ± 0.9	11.4 ± 0.5	0.2
Posttreatment blood loss (mL/kg)	63.3 ± 10.2	56.4 ± 9.7	43.5 ± 9.3	18.2 ± 8.8*	0.015 (One-way ANOVA)
Total resuscitation fluid (mL/kg)	178 ± 16	131 ± 13	134 ± 25	110 ± 15	0.1
Survival rate (%)	8.3 (1/12)	13.3 (2/15)	40 (6/15)	77 (10/13)*	0.001 (χ^2)
Survival time (min)	74 ± 13.9	74.7 ± 12.3	118.7 ± 15.2*	145 ± 15.5*	0.002 (Log rank)

Data are expressed as mean ± SEM and analyzed by different statistical tests.
* $p < 0.05$ vs. GZ or WS.

animals to survive the operation. In the FAST dressing group, application of the first dressing markedly reduced the initial bleeding, but it did not seal the arteriotomy site completely. The focal bleeding from this site was stopped when the second dressing was applied. The incidence of hemostasis achievement in this group increased from 15% to 77% (10 of 13) after application of the second FAST dressing (Table 3). The second treatment in other groups, however, had little or no effect on improving hemostasis. Stable hemostasis was achieved with one dressing application in eight experiments (1 in control, 2 in WS, 4 in CG, and 2 in FAST group); for all others, two consecutive dressings were applied to control the hemorrhage. The incidence of stable hemostasis achieved with the FAST dressing was significantly higher ($p < 0.05$) than in the WS and the control gauze groups.

MAP and Blood Loss

The average MAP of each group, which reflects the hemostatic conditions of the pigs during the experiment, is shown in Figure 2. There was a small decrease (~6 mm Hg) in MAP after hemodilution and hypothermia. The MAP at baseline, before injury (after hemodilution and hypothermia), and briefly after injury, where it dropped sharply, were not different among the groups. The MAP initially increased in response to fluid resuscitation in all groups but declined precipitously in the WS and CG groups as a result of continued hemorrhage. At 30 minutes and 60 minutes postinjury, the average MAP of CG- and FAST-treated animals were close to the target pressure (60 mm Hg) and were significantly higher than the other groups ($p < 0.05$).

The average pretreatment blood loss for all the animals was 11.9 mL/kg ± 0.4 mL/kg with no difference among groups (Table 3). The posttreatment blood loss was significantly different; the FAST dressing group had the least amount of blood loss, which was different from the WS and the gauze (GZ) groups (Table 3; Fig. 3). The total time that bleeding was stopped by the dressings was also significantly higher in the FAST group than in the other groups (Table 3).

Survival

Seventy-seven percent of FAST, 40% of CG, 13% of WS, and 8% of control (GZ) animals lived for the entire experiments
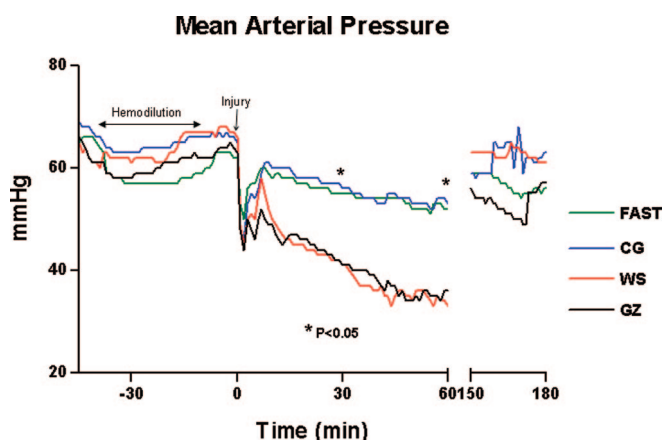
Figure 2. The average MAP of each group of pigs (survival and nonsurvival) treated with specific agents. The MAP in all groups stabilized and reached near baseline after completion of hemodilution. After hemostatic treatment and fluid resuscitation, the MAP in FAST and CG groups increased to a significantly ($p < 0.05$) higher level at 30 minutes and 60 minutes postinjury in comparison with WS- and GZ-treated animals. The MAP measured in the last 30 minute of experiments represents only the data from survived animals in each group.
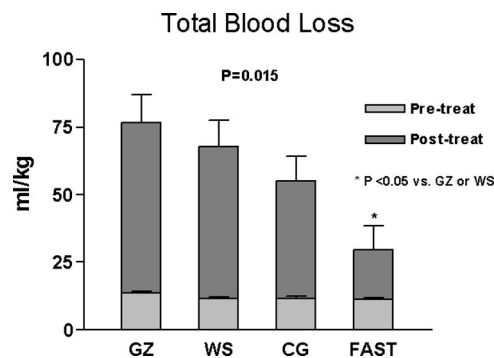
Figure 3. The average pretreatment and posttreatment blood losses of pigs treated with the agents. No difference was found in initial free bleeding among groups. The posttreatment blood loss was significantly less in the FAST group ($p < 0.05$) when compared with WS or gauze controls. The difference between FAST and CG groups was not statistically significant.

($p = 0.001$), with a final MAP of 60 mm Hg $\pm$ 1.5 mm Hg in all survivors. Among these groups, the FAST animals had a significantly higher survival rate than either WS- or GZ-treated pigs ($p < 0.05$). The Kaplan-Meier analysis of survival time for all groups is shown in Figure 4. The survival times of FAST (145 minutes) and CG (119 minutes) animals were significantly longer than the WS-treated (75 minutes) and the GZ-treated (74 minutes) pigs ($p < 0.05$; Table 3).

The final values of CBC, coagulation, and blood gas measurements at the conclusion of experiments are shown in Table 4. The coagulation parameters (PT, aPTT, and fibrinogen) could not be determined in the failed experiments (bleeding continued until death) because of excessive hemodilution of samples. The final hemoglobin, cell counts, and ABG values of the FAST dressing group remained closer to preinjury levels and were significantly higher than those of the WS and GZ groups.

The computed tomography images of survivor animals revealed limited blood flow through the arteries (8 of 10) that

Survival Time Analysis

Figure 4. Kaplan-Meier analysis of survival time of pigs treated with each agent. The FAST- and CG-treated animals lived significantly longer than the WS or control pigs treated with gauze. The difference between FAST and CG groups was not statistically significant.

were repaired with FAST dressings. Blood flow through the arteries treated by other agents was entirely blocked, but collateral vessels appeared to provide some flow to the distal tissues. Representative images of the vessels treated with FAST and CG dressings are shown in Figure 5 to illustrate this observation.

Morphologic and Histologic Assessment

At the conclusion of successful experiments, movement of the treated legs caused hemostatic failure and rebleeding in several surviving animals, particularly in the WS (2 of 2) and CG (2 of 6) groups, suggesting tenuous hemostasis and weak clot formation in coagulopathic animals treated with these agents. Among 10 survivors in FAST-treated group, the rebleeding occurred only in 2 pigs after walking simulation. Debridement of the WS-treated wounds to collect tissue samples also required ~2 L saline flush and significantly more effort than other agents.

The histologic changes for WS and CG treated vessels were similar to those seen in previous studies.[10,11] These included diffuse endothelial blebbing with multifocal endothelial cell loss in the arteries and mild neutrophils infiltration in adventitia of both arteries and veins. All nerve sections were normal with mild interstitial inflammation. The damage to endothelium, smooth muscle, and adventitia were more severe in WS-treated vessels than the other groups. The foreign materials (WS residues) were also found in the lumen of arteries, associated with multifocal thrombi, and on the adventitia of arteries and veins treated with WS. The tissue effects of FAST dressing were consistent with CG and GZ with the exceptions of increased neutrophilic inflammation and the presence of fibrin (left over of the dressing) in the vessels.

DISCUSSION

In this study, the efficacies of two mineral-based hemostatic agents, WS and CG, with potent clotting activities were examined under coagulopathic conditions. The function of these agents was compared with a biological dressing that
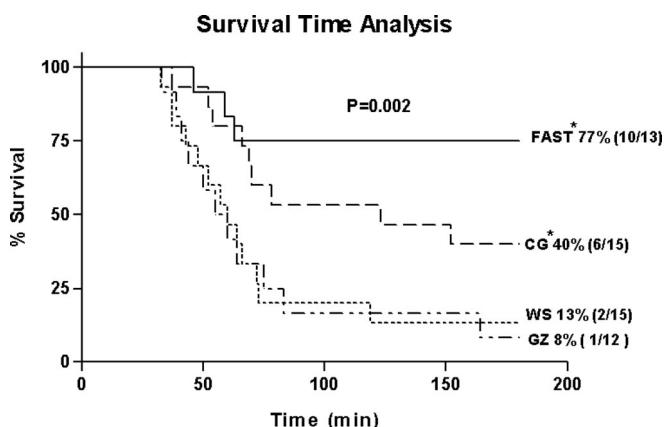
TABLE 4. Final Hematological Measurements of the Coagulopathic Pigs

Measure	Gauze (GZ; n = 12)	WoundStat (WS; n = 15)	Combat Gauze (CG; n = 15)	Fibrin Sealant (FAST; n = 13)	Overall p Value
Temperature (°C)	32.7 ± 0.1	32.5 ± 0.1	32.7 ± 0.1	32.9 ± 0	0.04
RBC ($10^6/\mu$L)	0.6 ± 0.1	0.6 ± 0.2	1.2 ± 0.2	1.7 ± 0.2*	<0.01
Hemoglobin (g/dL)	1 ± 0.2	1.1 ± 0.3	2.1 ± 0.4	2.9 ± 0.3*	<0.01
Platelet (1,000/μL)	38 ± 12	33 ± 9	66 ± 15	107 ± 13*	<0.01
PT (sec)[†]	21.3	19.3 ± 1.6	19.2 ± 0.4	19 ± 0.6	NS
aPTT (sec)[†]	25.8	27 ± 2.3	21.8 ± 1.0	23.7 ± 1	NS
Fibrinogen (mg/dL)[†]	56.5	40.3	80.0 ± 1.4	82.8 ± 1.9	NS
pH	7.55 ± 0.03	7.55 ± 0.02	7.49 ± 0.03	7.44 ± 0.02*	<0.01
Lactate (mM)	14.2 ± 1	13.2 ± 1.3	9 ± 1.7	5.7 ± 1.3*	<0.01
Base excess (mM)	−1.1 ± 0.7	−0.8 ± 1.1	2.5 ± 1.4	4.8 ± 1.3*	<0.01

Data are expressed as mean ± SEM and analyzed by one-way ANOVA test.
* $p < 0.05$ vs. WS or GZ.
† The PT, aPTT, and fibrinogen measurements represent only the results of the successful (survival) experiments. These values could not be measured in the final blood samples of the nonsurvivors because of excessive hemodilution (no clot formed).
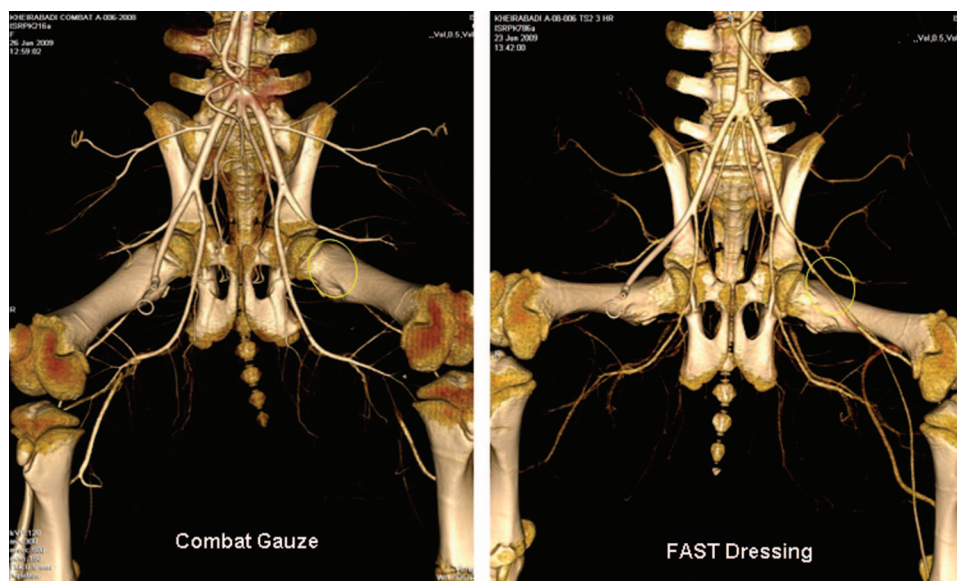
Figure 5. Representative computed tomography images of the arterial circulation in the hind legs of survivor pigs treated with CG and FAST dressings 3 hours after treatment. Note the blood flow obstruction at the injury site (yellow circled area) in the left artery treated with CG versus the patency of this vessel repaired with FAST dressing. The right femoral artery was cannulated by occlusive method.

contained the essential clotting proteins (fibrinogen and thrombin) and regular gauze. Previous studies in swine demonstrated successful treatment of a lethal arterial bleeding with these new agents under normal coagulation conditions. The results of this study, however, showed that the agents were not able to stop similar bleeding for 3 hours in the animals with preexisting coagulation deficiencies. These findings were expected for CG, whose hemostatic function is based solely on promoting clotting activity of the patient's own blood, but were unexpected for WS because of the additional tissue sealant property of WS clay observed in previous studies.[10,21] The in vitro treatment of coagulopathic blood with CG and WS accelerated the initial reaction and kinetic times of spontaneous clot formation but had no effect, or in case of WS even, reduced the strength of clot. This latter characteristic that depends on platelet function and fibrinogen concentration ultimately determines the hemostatic ability of the clot in the wound.

WS granules consist of a group of clay minerals known as smectite with aluminum phyllosilicate structure and small particle size (<2 μmol/L). The original WS formula, tested in an earlier study,[21] contained an absorbent polymer (polyacrylic acid) that was removed to improve the efficacy of the final product. In 2007, the manufacturing company (TraumaCure) received FDA clearance and marketed WS as a new hemostatic agent for temporary treatment of moderate to severe external bleeding in patients. This clearance was accomplished by demonstrating that WS was essentially equivalent to QuikClot, another previously approved hemostatic mineral (zeolite). Smectite is used in industries as filler in paints and rubber products and as a sealer and plasticizer in civil engineering for tunnel construction and mud drilling. When WS is poured in a bleeding wound, the granules rapidly absorb water, swell, and form a viscous clay material that has high plasticity, conformity, and sealing properties. With moderate pressure, the clay material adheres to the tissues and seals the bleeding sites in the wound. This process appeared to be the main mechanism by which WS produced immediate hemostasis when it was applied to severely bleeding wounds.[10,21] In addition, the smectite granules carry negative electrostatic charges that activate the intrinsic pathway and accelerate the clotting reaction in normal blood, as was shown in earlier in vitro (TEG) experiments.[10]

The inherent sealant properties of WS clay suggested an additional advantage of WS for treatment of coagulopathic bleeding. This hypothesis was supported by some in vitro and in vivo (personal communication) data that were reported by the company. For example, addition of WS to fourfold diluted blood shortened the clotting times equal to the values of undiluted blood samples.[14] WS also normalized the prolonged clotting times of the acquired hemophiliac blood specimen, which were previously incubated with factor VIII and IX antibodies.[16] The failure of WS clay to adhere to underlying tissues and produce hemostasis in this study suggests that in previous experiments, the clots that were formed instantly after addition of WS to the blood mediated the binding of the clay material to the tissues and provided hemostasis. Therefore, the normal clotting activity of blood was essential for hemostatic activity of WS. Another possible explanation is that the presence of HES in the diluted blood of coagulopathic pigs interfered with the adherence of WS to the tissues and prevented sealing of the bleeding sites.

Application of WS granules to stop bleeding in wounds from major vascular injuries was recently found to be associated with significant side effects.[22] Despite extensive de-

bridement of the wounds after treatment with WS, the residues of smectite minerals remained in the lumen of the vessels and produced occlusive thrombosis when blood flow was restored in the vessels. WS granules also passed through venous circulation and embolized in the lung tissues. An earlier in vitro study also reported specific cytotoxicity of smectite minerals (bentonite and montmorillonite) toward human umbilical veins endothelial cells.[23] Given these potential side effects, the risk of using WS may surpass the benefits of this agent for treating normal (noncoagulopathic) bleeding, particularly when safer agents (e.g., CG) are currently available. However, if WS could be proven to be the only product that is effective against coagulopathic bleeding, then its use would be justified in coagulopathic patients with life-threatening hemorrhaging. The results of this study showed that WS is no more effective than regular gauze to control vascular bleeding in coagulopathic subjects. WS is a commercially available product and can be purchased and used without prescription. Although we have no knowledge of the use this product in civilian communities, the purchase and application of this hemostatic agent was permanently halted in the US Military (April 2009) after its side effects were revealed in preclinical studies.[22,24]

Although there was no statistically significant difference in most but one main outcome (survival time, Table 3), a trend toward better performance of CG when compared with GZ and WS was noted. This dressing was as good as FAST dressing in control of hemorrhage and maintaining MAP during the first hour after application. CG consists of a roll of surgical gauze (4 yards long, 3 in wide) impregnated with kaolin white powder that is a potent contact (intrinsic) pathway activating agent. Kaolin is also a clay mineral with aluminum phyllosilicate structure, but it has different sets of cations. In addition to its use in cosmetics and in the ceramic industries, it is used as an antidiarrhea agent in medicine. Kaolin comprises ~10% of the product weight and, combined with the gauze product, is a simple and effective means of treating a wound and stopping bleeding while leaving behind no residues to cause thrombosis.[11] This dressing is now distributed among the US forces for use as the first line of treatment for life-threatening hemorrhage on the battlefield.

Chitosan-based products were not included in this study because these products either consistently failed (HemCon bandage) to achieve hemostasis or had unpredictable results (Celox) when they were tested in the same arterial injury model but in the normal pigs. Given the limited efficacy of these agents under normal coagulation conditions, it seemed unlikely that these products would be effective against similar bleeding under coagulopathic conditions.

The results of this study may also imply the need for a new class of hemostatic agent that can function independently of host coagulation activity. Such a product will be particularly beneficial to trauma patients who develop early coagulopathy at the point of injury and those patients acquiring coagulopathy after arriving at hospitals as result of excessive surgical bleeding and resuscitation therapy. The most successful hemostatic agent in our challenging model was a prototype biological dressing composed of plasma-derived (human) fibrinogen and thrombin, which was significantly more effective than GZ and WS, and consistently demonstrated superior performance than CG. Different versions of this type of dressing have been introduced in the past and were shown to be effective in stopping severe venous bleeding (caused by grade V liver injury) in coagulopathic swine.[18,25] The hemostatic reaction occurs when the freeze-dried proteins on these dressing are exposed to blood or liquid, resulting in activation of thrombin, polymerization of fibrinogen, and formation of dense fibrin that binds to injured tissues and secures hemostasis. Unlike the other products, which function by inducing clotting of the patient's blood, the FAST dressing achieved hemostasis without occluding the injured vessel. It is interesting to note that an earlier version of this product accomplished this same feat when used on a Soldier with a similar peripheral arterial injury in combat.[26]

Fibrinogen-based dressings are fully absorbable and intended for treatment of internal or external bleeding in prehospital or hospital environments. Unlike hemostatic devices (e.g., CG and WS), the safety and efficacy of these biological dressings must be examined in lengthy clinical trials (for FDA approval) requiring substantial initial investment. The cost of producing these dressings with purified plasma proteins is also substantially higher than mineral- or chitosan-based products, making the final product perhaps 5 to 10 times more expensive than the other agents mentioned. However, these dressings offer potential advantages that may increase survival, improve the patient's recovery and in the long run result in a substantial savings. For example, the use of these dressings can reduce the need for multiple transfusions in some trauma patients during surgery and avoid the associated side effects or eliminate a second operation necessary to remove nonabsorbable materials used to control internal bleeding in patients. Obviously, future clinical studies will prove to what degree these potential advantages will truly benefit the patients. Another advantage of the FAST dressing, noted in this study, was its ability to maintain blood flow to the distal tissues. While the dressing plugged the hole and stopped the hemorrhage, it did not obstruct blood flow through the vessels, a beneficial effect in minimizing ischemic injuries. Previously, we observed complete occlusion of the injured vessels with only limited collateral flow when WS, CG, or other agents were used to stop bleeding in this model.[10,11]

The main limitation of this study is perhaps the model that was used to test these products. The focal arterial injury in our model mimics a gunshot wound to a major artery in the groin area and does not represent classical coagulopathic bleeding, which involves persistent and diffuse bleeding from a large area of injuries. However, early coagulopathy has been shown to develop in some trauma patients with shock and massive tissue injury before they arrive to the hospital or receive significant fluid resuscitation. At least one-fourth of trauma patients have been diagnosed with this type of coagulopathy on arrival at the hospital.[27,28] The prehospital control of bleeding in these patients, even with focal injuries, may be much more difficult than in patients without coagulopathy.

Although coagulopathy in our model is produced by an entirely different mechanism (hemodilution and hypothermia), it still represents a significant deficiency in coagulation (30% prolongation of PT time and 28% decrease in clot strength) that makes the control of bleeding very difficult with ordinary hemostatic agents.[9] Our group and others have not been able to develop a trauma-/shock-related coagulopathy (Acute Traumatic Coagulopathy) in pigs, which might be ideal for hemostatic dressing studies. Even in a polytrauma model that include a femur fracture and Grade V liver injury with uncontrolled hemorrhage, a controlled hemorrhage and fluid resuscitation with saline ($3\times$ volumes) are needed to produce coagulopathy (dilutional) in pigs.

Another reason for selecting this injury model was our past experience with the model in which both CG and WS were able to successfully stop arterial bleeding. Addition of preexisting coagulopathy to the model allowed us to see the benefit of these agents to control similar hemorrhage under coagulopathic conditions. Ideally, coagulopathy should be induced after the injury to better mimic the normal injury sequence seen in humans. However, this represents a technical limitation that cannot be overcome in these experimental studies. Equal degrees of coagulopathy cannot be induced by fluid administration and hypothermia in the animals that are profusely bleeding (uncontrolled arterial hemorrhage). Such procedure can lead to exsanguination of subjects before hemostatic dressings are applied. The reproducible preexisting coagulopathy that was produced in this study presented a very difficult and challenging bleeding condition that was not impossible to overcome as FAST dressings were able to stop this hemorrhage and prevent death in the majority (77%) of animals. Future studies are planned to develop a new hemorrhage model involving a large wound with significant tissue loss and multiple small vessel injuries in coagulopathic animals to test agents such as CG and chitosan-based dressings with tissue adhesive properties for control of coagulopathic bleeding.

In summary, neither WS nor CG was able to stop arterial bleeding for 3 hours in most pigs with preexisting dilutional hypothermia coagulopathy. The same injuries, however, were successfully treated with these agents in noncoagulopathic animals in previous studies. These findings were expected for CG, whose hemostatic function is solely based on promoting clotting activity of host blood, but were unexpected for WS because of the strong tissue sealant properties of this clay mineral seen in earlier studies. CG, however, was partially effective against the hemorrhage as it maintained MAP near baseline level during the first hour after application. The FAST dressing composed of human clotting proteins was the only agent that stopped most of the coagulopathic bleeding and prevented exsanguination. The effectiveness of these dressings may be due to the exogenous delivery of concentrated fibrinogen and thrombin to the wound, which bypasses the coagulopathy and provides hemostasis independently from the coagulation status of the subjects.

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DISCUSSION

Dr. Martin Schreiber (Portland, Oregon): Good morning. Dr. Kheirabadi and his colleagues from the ISR present another study in a long line of studies that evaluate new hemostatic dressings. Similar to the prior work, this study is extremely well thought out and executed and the manuscript is very well written.

They have shown that the new FAST dressing and Combat Gauze are clearly superior to WoundStat and a novel control gauze in a coagulopathic model. The authors have also shown that the FAST dressing is probably superior to Combat Gauze. I have a number of questions and comments.

Number one, why was LR used for spleen replacement and Hextend for the one-to-one isovolemic hemodilution? It's a huge amount of Hextend that's probably never clinically used either in civilian or military practice and for this reason, I have to ask, is this model clinically relevant?

Number two, Combat Gauze is very thin and we have found it takes significantly longer to pack than other dressings, like standard gauze. Could the time it takes to pack the dressing affect your results and also, I would point out that the hold time on this was two minutes and no medic in his right mind is going to hold a dressing for two minutes in a combat under fire situation and in my opinion, the hold time should be either zero or ten seconds or a period of time that would be reasonable for a medic under fire.

I think it's important to point out that the gauze used in this study was not standard gauze. It contained rayon and polyester and it serves as a control for Combat Gauze. We have found in our studies that the 3,000-year-old standard gauze is very effective in our models and sometimes studies like this can be misleading because the dressing under study is not being compared to a common standard.

This was not a blinded study and it's very difficult to blind when the dressings are so different. However, the person who holds the pressure for two minutes could be blinded, to avoid bias. Why don't you blind the person who holds pressure?

The manuscript states that animals in whom bleeding could not be stopped with initial application of the dressing were excluded and there was one animal like this in the FAST group. Why were these animals excluded? That seems like a very important endpoint of the study and if you include that animal, it changes the results significantly.

Finally, your data suggests that the FAST dressing is more effective and logistically superior to Combat Gauze in coagulopathic environments. What will you recommend to Tactical Combat Casualty Care, which is the group that decides what dressings are used on the battlefield? Will you recommend that FAST replace Combat Gauze or that FAST be added to Combat Gauze for use in obviously coagulopathic patients or do you think more data is needed?

I would like to thank the organizers of EAST for the honor of the podium and I would like to congratulate the authors on their excellent work and their dedicated efforts to save the lives of our injured war fighters.

Dr. Bijan Kheirabadi (Kingsbury, Texas): Thank you, Dr. Schreiber. Thanks for your remarks and your questions. I'll try to answer all of them. First of all, as we described in our manuscript, one of the limitation of this study was the model that we used.

As you know, we and other groups have been trying to develop what is considered to be a clinically relevant coagulopathy which would be an acute traumatic coagulopathy. Unfortunately, that's very hard to reproduce in pigs. As soon as we create multiple injuries/hemorrhage and provide minimum fluid replacement, the animals' blood actually becomes hypercoagulable rather than hypocoagulable.

The coagulopathic model that we used here is the model developed almost twenty years ago by Dr. Holcomb and represents a condition where the pig's blood does not clot normally, though I admit removing 50 percent of blood volume and replacing it with Hextend, is not clinically relevant, but it is the only way we can develop a reproducible coagulopathy in the pig and test various products. If we had not used Hextend and for instance used crystalloid instead, the animals would have developed edema, become hemodynamically unstable and could not tolerate the additional bleeding afterwards for testing of the dressings. Although this model is not ideal, it still provides a condition that coagulation is significantly diminished allowing us to test the agents under coagulopathic conditions.

Regarding the time of application, I do agree with you that Combat Gauze is a thin material and it takes time (one minute or so) to pack the wound with it but we did the same procedure for all other products. For instance, using regular gauze, we slowed down that process so the application time will be the same.

The two-minute compression, I totally agree with you that it may be too long for the battlefield situation. If we find other products that work effectively in a shorter time, we certainly would like to test and recommend them. With Combat Gauze, the two-minute compression is the minimum time requirement to develop hemostasis and for that matter, the FAST dressing requires the same compression time.

Regarding the blindness of the study, yes, this study was not entirely blinded. However, to the extent that was possible, the study was blinded. All the daily experiments were pre-designed ahead of time on a random basis without my knowledge or the OR staff. When we came to the operating room, we had no idea what product would be tested that day until the time that the injury was done and the bleeding was created and then I was handed the assigned product to apply. The idea that perhaps compression can be done by another individual, is an excellent suggestion, however in this particular case, with the FAST dressing, it could not be done. The reason for that is the fibrinogen material in that dressing; as soon as you put the dressing on the wound, fibrinogen begin to dissolve and polymerize by thrombin, forming a thin adhesive fibrin layer. If you take the hand off to change to someone else to provide compression, the material will dislodge and the fibrin bonding to the tissue will be disrupted and it will not be reattached with more pressure. Whoever applies the FAST dressing must provide compression too.

Regarding the exclusion of one animal in FAST dressing, we had two animals in FAST dressing that were excluded. Both of them met our exclusion criteria. One of our exclusion criteria was that during fluid resuscitation, the mean arterial pressure must return to 65 mmHg and remain in that level when the treatment is successful. In one successful experiment with FAST dressing, the animal blood pressure did not reach to 65 mmHg with resuscitation and therefore that animal was excluded. Another criteria was that given enough pressure and complete wound coverage, the bleeding must be stopped during 2-min compression to allow the hemostasis to occur, otherwise the experiment must be excluded. In another case using FAST, bleeding could not be stopped during compression and therefore that animal was

excluded. Even if these two animals were included in the study, the survival rate for FAST group would have been eleven out of fifteen (73%), which is not different than the present one, ten out of thirteen (77%).

With respect to the type of gauze that we used, yes, we used the raw material for Combat Gauze, to be sure that if we see an advantage with Combat Gauze, it can be attributed to its active agent (kaolin) and not to the gauze material of this dressing. Although the gauze that we used was not a regular cotton gauze, it was intended as a negative control material and served that purpose in this study.

With respect to our recommendation to Tactical Combat Casualty, that is going to be held back until we actually have an FDA approved fibrinogen dressing. FAST dressing, unlike all other dressings, is considered a biological material and therefore must go through clinical trials for safety and efficacy before approval. It is still too early for this product to become marketable. None of the other dressings have gone through these types of testing because they are considered to be medical devices.

Is FAST dressing a material to replace everything else? I don't think so. I think many of the bleedings can be stopped and are being stopped with Combat Gauze or similar materials and so if there is a forum to use FAST dressing, it might be in a special situation, where the other dressings are ineffective or patients have significant coagulopathy. I think the main application of this dressing might be in the combat support hospitals where coagulopathic casualties are brought in. The absorbable FAST dressing may be used effectively for damage control surgeries to pack the injured organs and provide hemostasis. It may be helpful to medics in special circumstances, but it is mainly going to be in the hands of surgeons and used in the OR to stop internal bleedings.